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The Contributions of UVA and UVB to Connective Tissue Damage in Hairless Mice

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UVA, in high-dose single exposures, can, like UVB, be deleterious to skin. Dermal damage resulting from chronic exposure to UVA has not been studied. To investigate the long-term effects, we irradiated albino hairless mice for 30–34 weeks with UVA radiation, alone, from two sources with differing spectral qualities, and in combination with UVB as solar-simulating radiation. The results were compared to UVB alone.

Like UVB, the UVA waveband, especially that with a spectral distribution similar to solar UVA, caused elastic fiber damage, increased glycosaminoglycan levels, and produced hypertrophy of deep dermal tissues. There were, however, striking differences between UVB- and UVA-irradiated skin. A combination of UVA and UVB summated the effects of both wavebands. Substantial protection against these effects was afforded by a broad-spectrum sunscreen.

It is well established that UVB radiation (280–315 nm) can cause erythema, skin cancer, and dermal connective tissue damage [1]. Recent reports indicate that UVA (315–400 nm), too, is erythemogenic [2,3] and carcinogenic [4,5] when the dose is a thousandfold higher than UVB. Even greater doses (>20,000 J/cm^2) have produced elastosis in naked (Ng/−) mice [6]. In humans, after only 2.5 minimal erythema doses (MEDs), endothelial cell enlargement, extravasation of blood cells, and perivenular neutrophil infiltrates [7] are accompanied by increased concentrations of mediators of inflammation such as arachidonic acid, prostaglandins, and histamine [8]. UVA also comprises the action spectra of the great majority of photosensitizing chemicals and drugs [9] and it is implicated in solar urticaria [10]. UVA can augment, either additively [11] or synergistically [12,13], the acute and chronic effects of UVB. A solar-simulating combination of UVA and UVB is tumorigenic in hairless mice [14] and this can be augmented with added UVA [15]. However, the extent to which UVA alone can induce dermal damage has not been studied.

UVA cannot be perfunctorily ignored since it is present year-round, all day, and at doses that may be 100–1000 times greater than UVB. About 40–50% of UVA is transmitted by Caucasian epidermis compared to 10–30% of UVB [16] and it is more deeply penetrating, making it possible for UVA to play a role in dermal photodamage. In the present study we have addressed this hypothesis by examining the role of UVA alone, in comparison to UVB alone, and in combination with UVB on dermal damage in hairless mice.

MATERIALS AND METHODS

Animals and Treatment Groups

Albino Skh:hairless-1 female mice, 6–8 weeks old, were obtained from the Skin and Cancer Hospital of Temple University Health Sciences Center, Philadelphia, Pennsylvania. They were housed individually in stainless steel cages. Groups of 12 animals each were distributed into the following irradiation categories: (1) UVB; (2) UVA-xenon (low dose); (3) UVA-black light (UVA-BL) (high dose); (4) solar-simulating radiation (SSR); (5) SSR and broad-spectrum sunscreen (BS-SS); (6) unirradiated controls.

Radiation Sources and Schedules

The UVB source was a bank of 9 Westinghouse FS20 "sunlamps." A dose of 0.07 J/cm^2, the equivalent of 2 human MEDs, was given thrice weekly for 30 weeks, yielding a total dose of ~5.6 J/cm^2. Two differing UVA spectra, obtained from different sources, were used (Fig 1). The xenon lamp used for the low dose (UVA-xenon) was a forced air cooled 5000 W compact arc solar simulator (Kratos Analytical Instruments, Ramsey, New Jersey). The collimated beam was passed through a water filter before impinging on a 45° UV-reflecting dichroic mirror and finally through a 2-mm Schott WG 345 filter (50% cutoff at about 345 nm). A dose of 35 J/cm^2, obtained with 80 min of irradiation, was given thrice weekly for 34 weeks, yielding a total dose of ~3000 J/cm^2. Average UVA irradiance at skin level was 7.5 mW/cm^2 and UVB irradiance (<315 nm) was 7.2 μW/cm^2, 85% of which was between 300 and 315 nm. A bank of 8 General Electric F20T 12/BL black lights (peak irradiance ~365 nm) was used for the high dose (UVA-BL). The radiation was filtered through a 0.15 mm-thick sheet of Mylar (50% cutoff at about 345 nm) which was replaced at 4-week intervals to avoid effects due to photodegradation. A dose of 135 J/cm^2, obtained with 16 h of irradiation, was given thrice weekly for 34 weeks, yielding a total of ~13,000 J/cm^2. SSR was obtained from the xenon lamp by filtering the beam through a 1-mm Schott WG 320 filter, providing spectral irradiance similar to solar UV radiation. Each 30-min exposure supplied ~.07 J/cm^2 UVB and ~7.0 J/cm^2 UVA. These were given thrice weekly for 34 weeks, yielding totals of ~5.6 J/cm^2 UVB and ~560 J/cm^2 UVA. In addition, following each SSR exposure, 30–35 J/cm^2 supplemental UVA was given by means of the Mylar-filtered black lights, bringing the total dose of UVA to ~3400 J/cm^2. In each group, to avoid burning, the initial doses were low and were gradually increased to full strength.

Flux was measured weekly with an IL 700A Research Radiometer (International Light, Inc., Newburyport, Massachusetts). The UVB sensor had a peak sensitivity at ~290 nm, while that of the UVA was at ~360 nm.

The spectral irradiance, at skin level, of both UVA sources was determined by an International Light Spectroradiometer System (Model 782). Measurements were obtained at 10-nm intervals, beginning at 280 nm.

Sunscreen

The broad-spectrum sunscreen (BS-SS) with a sun protection factor (SPF) of 15 (Supershade 15 [Coppertone] Schering-Plough Corp.) containing 7% octyl dimethyl PABA and 3% oxybenzone was applied to the dorsal trunk, immediately prior to irradiation in 25-μl aliquots, yielding a surface dose of approximately 2.5 μl/cm^2.

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Abbreviations:
- BS-SS: broad-spectrum sunscreen
- D-E: dermal-epidermal (junction)
- GAG: glycosaminoglycan
- MED: minimal erythema dose
- SPF: sun protection factor
- SSR: solar-simulating radiation
- UVA-BL: UVA radiation with spectrum produced by Mylar-filtered black lights
- UVA-xenon: UVA radiation with spectrum produced by WG 345 filtered xenon lamp

Histology

Half of the animals in each group were sacrificed at the end of the irradiation period. Strips of dorsal skin, 2 cm long, were fixed in 10% buffered formalin, embedded in paraffin, and sectioned at 7–10 μm. The stains were: H & E, Luna's aldehyde fuchsin for elastic fibers [17], Van Gieson's for collagen, Mowry's colloidal iron for glycosaminoglycans (GAGs), alcian blue at pH 2.5 for hyaluronic acid and at pH 1.0 for sulfated GAGs. The sections were read in a coded manner.

RESULTS

UVA Effects: A comparison with UVB

UVA-xenon irradiated group: Normally, hairless mouse skin shows 1–2 rows of large, horn-containing cysts in the deep dermis (Fig 2*a*). UVB caused an increase to 3–5 rows (Fig 2*b*), presumably by stimulating the proliferation of undeveloped epithelial nests. UVA, with a spectral distribution similar to that of sunlight, induced even greater proliferation to 6–7 rows (Fig 2*c*).

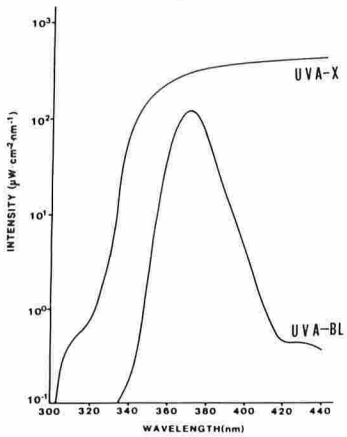

FIG 1. Spectral irradiance at skin level. Spectral power distribution of WG 345-filtered xenon lamp *(UVA-X)*; spectral power distribution of Mylar-filtered black lamps *(UVA-BL)*.

The expanding cyst compartment of UVA-irradiated skin often compressed the overlying collagen into a narrow band, with bundles in parallel array (Fig 2*c*). Nevertheless, the collagen showed no morphologic damage by Van Gieson's staining. In contrast, UVB produced a thickening of the upper dermis with dense accumulations of parallel collagen bundles. These stained feebly with Van Gieson's and were judged to be damaged (Fig 3*a*).

UVA and UVB differed also with regard to their effects on dermal cells. With UVA, the inflammatory infiltrate was negligible (Fig 4*a*); mast cells were of normal size and distribution, remaining mainly in the lower dermis among the cyst-induced granulomatous reaction. UVB provoked a massive inflammatory infiltrate in which lymphocytes predominated but which included a few eosinophils and neutrophils (Fig 4*b*). Mast cells, numerous in the upper dermis, were large and engorged with darkly stained granules. They were often closely associated with aggregates of elastosis (Fig 3*b*).

The marked UVB-induced elastotic changes were characterized by densely compacted tangles of thickened fibers deposited in the upper dermis (Fig 3*b*). In contrast, the elastosis induced by UVA was distributed more deeply into the dermis. The fibers were finer and less dense. In short, UVA elastosis was much more delicate (Fig 3*c*).

GAGs, normally very sparse in the hairless mouse, were clearly increased by both UVA and UVB. All 3 histochemical stains showed UVB to be the more effective inducer. With Mowry's stain, UVB-induced GAGs appeared as blue-stippled deposits in the upper dermis (Fig 3*d*). The UVA-induced deposits were narrower and often included a dense, darker blue accumulation at the dermal-epidermal (D-E) junction (Fig 3*e*). The entire upper dermis had a bluish cast, in contrast to UVB specimens where collagen bundles remained bright red. Hyaluronic acid was greatly increased throughout the upper dermis

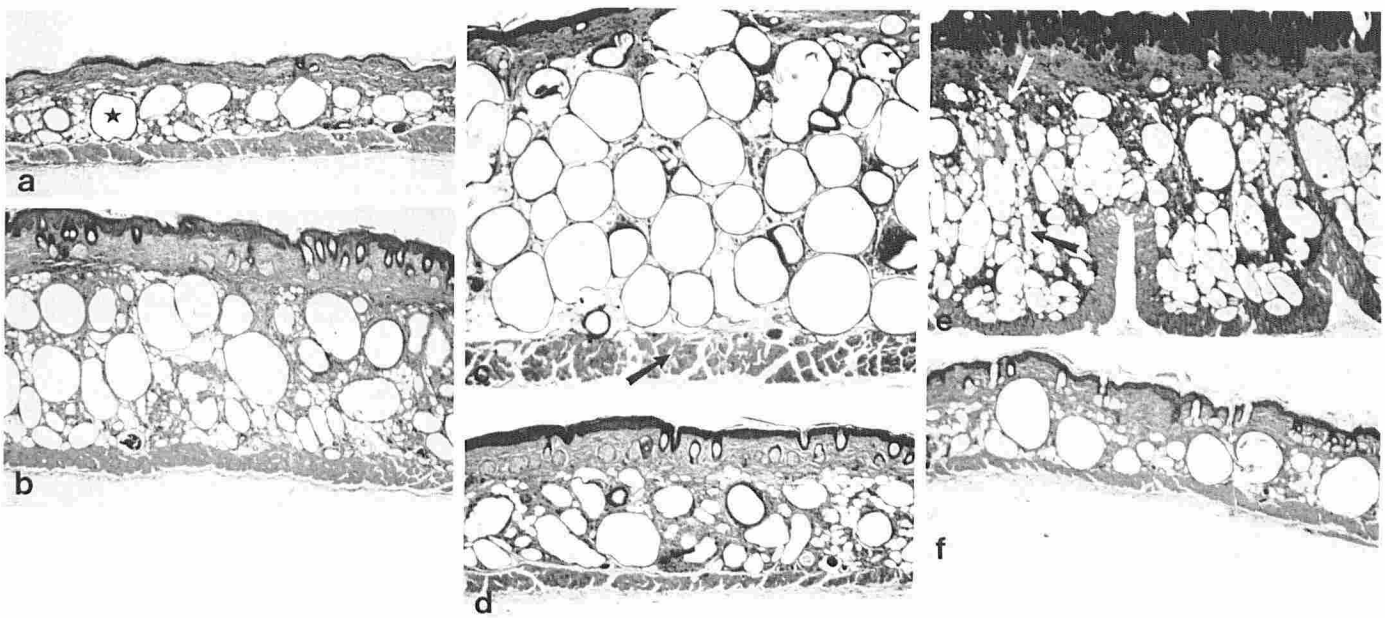

FIG 2. *a*, Normal hairless mouse skin. There are 1–2 rows of horn-containing dermal cysts *(asterisk)* which appear empty due to histologic processing. H & E, × 26.

b, UVB irradiation. Dermal cysts are enlarged and proliferated to form 3–5 rows, adding significantly to skin thickness. H & E, × 26.

c, UVA-xenon irradiation. The greatly enlarged, proliferated dermal cysts occupy 6–7 rows, increasing skin thickness more than 3-fold. The panniculus carnosus *(arrow)* is also thicker. Note compression of the collagen-containing upper dermis. H & E, × 26.

d, UVA-BL irradiation. There is only a moderate proliferation of cysts which are smaller than those of the UVA-xenon specimens. H & E, × 26.

e, SSR. Dermal cysts, although not uniformly enlarged, are proliferated up to 6 rows. The upward folding of the thickened panniculus carnosus resembles that of UVA-xenon irradiated specimens. There are increased numbers of lipocytes *(arrow)* among the cysts. H & E, × 26.

f, SSR and BS-SS. Almost indistinguishable from normal skin, the BS-SS protected skin has no cyst proliferation. Only a mild epidermal hyperplasia provides evidence of the irradiation. H & E, × 26.

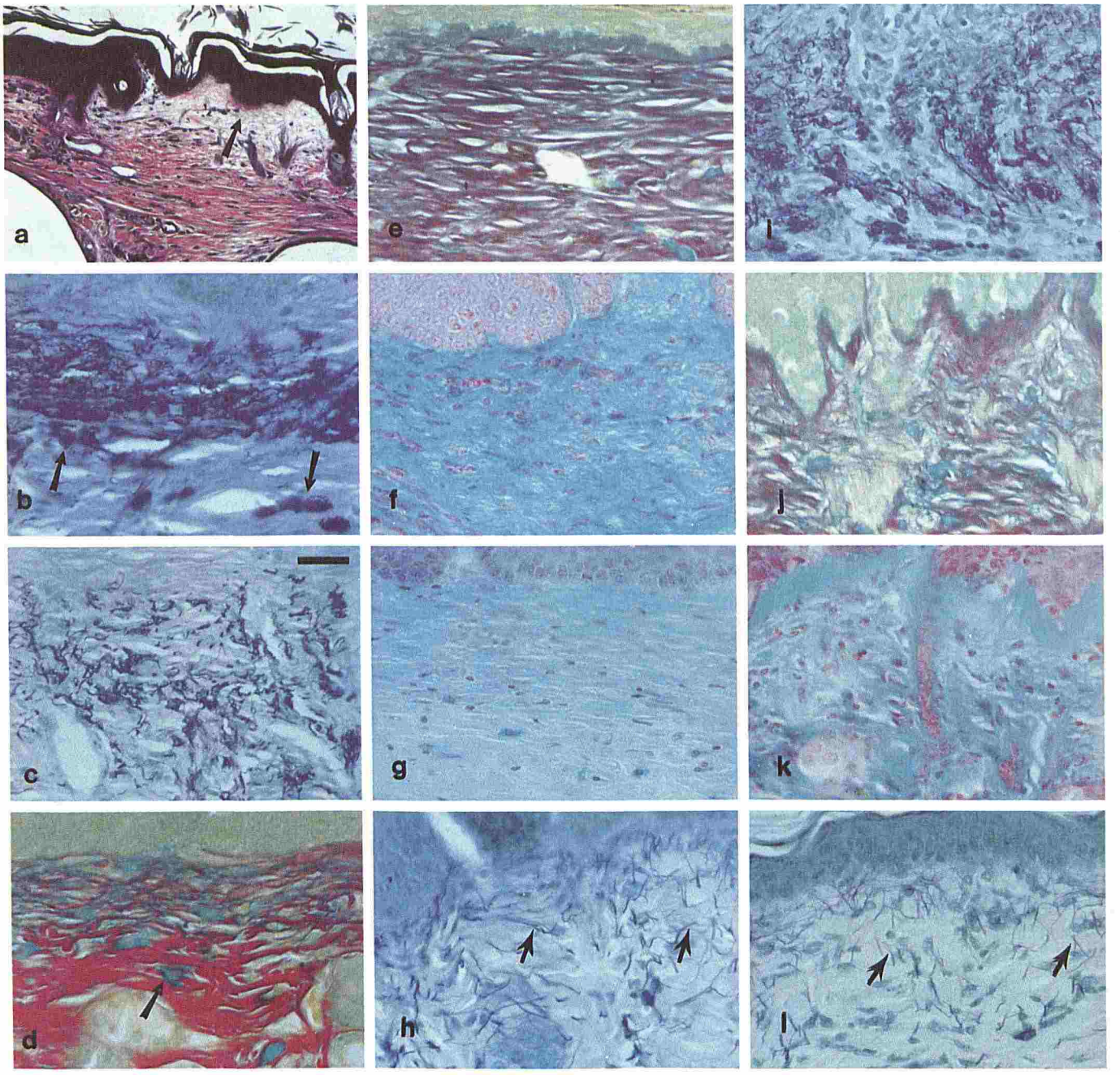

FIG 3. Special stains.

a, UVB irradiation. Loss of avidity for the stain *(arrow)* provides evidence for damage to mature collagen. Van Gieson's stain, × 115.

b, UVB irradiation. Dense accretions of thickened, tangled elastic fibers are massed in the subepidermal dermis. Large mast cells *(arrows)* are abundant in this area. Luna's stain, × 290.

c, UVA-xenon irradiation. The elastotic deposits are less dense than with UVB, but often extend deeply into the upper dermis. D-E junction is indicated by *bar*. Mast cells are not conspicuously present. Luna's stain, × 290.

d, UVB irradiation. Increased amounts of GAGs appear as blue-stippled deposits in the uppermost dermis. Mast cells *(arrow)* also stain blue. Mowry's stain, × 290.

e, UVA-xenon irradiation. Narrow regions of blue-stippled GAG deposits are difficult to visualize because of the bluish hue of the collagen. The more dense deposits at the D-E junction are obvious. Mowry's stain, × 290.

f, UVB irradiation. Strongly positive for hyaluronic acid, the entire upper dermis is a deep blue. Normal mouse dermis is a pale bluish pink. Alcian blue, pH 2.5, × 290.

g, UVA-xenon irradiation. A moderate increase in hyaluronic acid throughout the upper dermis. Alcian blue, pH 2.5, × 290.

h, UVA-BL irradiation. Mild elastic fiber hyperplasia with slight thickening of fibers *(arrows)*. Luna's stain, × 290.

i, SSR. Diffuse elastosis beginning at the D-E junction and extending well into the upper dermis. Mast cells are abundant. Luna's stain, × 290.

j, SSR. The staining pattern combined those of UVB and UVA. Stippled blue GAG deposits are present in the upper dermis while deposits at the D-E junction are more dense. Collagen bundles have a bluish hue. Mowry's stain, × 290.

k, SSR. Strongly positive staining for hyaluronic acid throughout the dermis with increased deposition at the D-E junction. Alcian blue, pH 2.5, × 290.

l, SSR and BS-SS. Very mild elastic fiber hyperplasia characterized by what appears to be fine short strands *(arrows)*. Luna's stain, × 290.

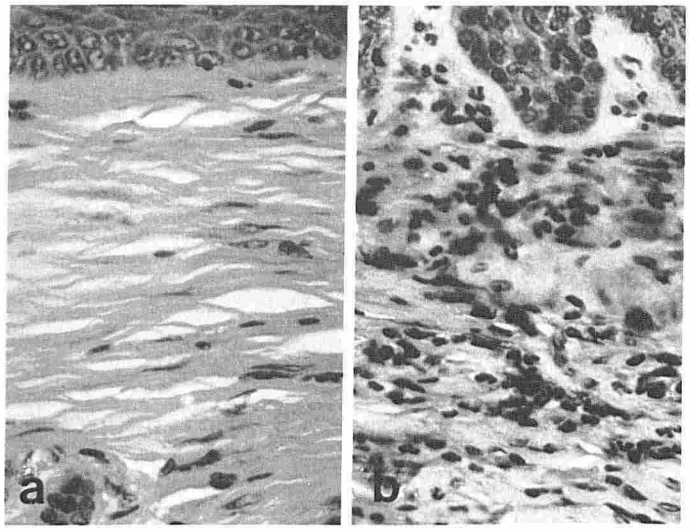

FIG 4. Dermal cellularity. *a*, UVA-xenon irradiation. With H & E stain, fibroblasts are the major cellular component visible in the subepidermal dermis. No inflammatory infiltrate is evoked by chronic UVA irradiation. H & E, × 260. *b*, UVB irradiation. There is an infiltrate consisting of lymphocytes, eosinophils, neutrophils, and mast cells. H & E, × 260.

by UVB (Fig 3*f*) and less so by UVA (Fig 3*g*). Sulfated GAGs behaved similarly, but the increases were less striking.

The panniculus carnosus, normally 50–110 μm thick, increased to about 250 μm with UVA (Fig 2*c*), often being thrown into folds. In other places the proliferating dermal cysts invaded the panniculus, disrupting it and compressing it to narrow dimensions. UVB produced less, but more uniform thickening (~175 μm) with little disruption by cysts (Fig 2*b*).

Reduplication of the subpannicular elastic sheath was similar with both UVB and UVA; 5–6 thickened, overlapping strands compared to the normal 3–4.

UVA-BL irradiated group: In contrast to UVA-xenon specimens, those from the UVA-BL group sustained far less damage although irradiated with more than 4-fold higher doses of UVA. The dermis was moderately thickened, mainly because of a slight, variable proliferation of cysts (2–3 rows) (Fig 2*d*). Despite some increase in collagen, indicated by a mild thickening of the uppermost dermis, the bundles remained in random array in comparison to the packed, parallel configuration of the UVA-xenon group. Van Gieson's stain showed most of the collagen to be undamaged except for a few tiny foci in the subepidermal dermis. As in the UVA-xenon group, the inflammatory infiltrate was negligible and the mast cell population was not altered.

In contrast to both UVA-xenon- and UVB-irradiated specimens, elastosis was insignificant. Elastic fibers were only mildly hyperplastic with little thickening (Fig 3*h*). With regard to GAGs, Mowry's stain showed a striking increase, comparable to that of UVA-xenon specimens (see Fig 3*e*), and included the dense, darkly stained accumulation at the D-E junction. However, hyaluronic acid and sulfated GAGs were only slightly increased. There was no localization at the D-E junction.

The panniculus carnosus was only slightly thickened, up to ~150 μm (Fig 2*d*), without reduplication of the elastic sheath.

Other Effects of UVA

UVA, of both spectral qualities, was mildly tumorigenic. At week 45, 2 of the 6 surviving animals exposed to black light had a total of 3 papillomas; histologically, these were early squamous cell carcinomas. Two of the six surviving animals exposed to the xenon source developed a total of 3 pedunculated papillomas that were benign at the time of sacrifice (week 45). It is noteworthy that all animals in the UVA-xenon group suffered necrosis of approximately two-thirds of the distal portion of the ears. This occurred in no other group.

Solar-Simulating Radiation

In many of its effects, SSR showed the influences of both UVB and UVA, while in others, the result was like UVB alone. Dermal thickness was greater than with UVB, owing to greater cyst proliferation to 4–6 rows (Fig 2*e*).

Collagen changes were comparable to UVB alone; the thickened dermis contained parallel bundles staining poorly with Van Gieson's (see Fig 3*a*). As with UVB, the upper dermis was extremely cellular with fibroplasia and a severe inflammatory infiltrate. Mast cell appearance and distribution were also similar to UVB specimens.

Elastosis was severe, with a summation of the effects of UVA and UVB. It tended to begin just beneath the D-E junction and extended deeply into the dermis. The fibers were more delicate than in UVB elastosis (Fig 3*i*).

According to the 3 histochemical stains, GAGs were equal to or slightly increased compared to UVB alone. As with UVA alone, Mowry's revealed darkly stained material at the D-E junction (Fig 3*j*). A similar deposit was often seen with alcian blue at both pHs (Fig 3*k*).

The panniculus was thickened up to ~240 μm. As in the UVA-xenon specimens, it was folded upward in places (Fig 2*e*) and disrupted by cysts in others. The elastic sheath showed additive effects of both irradiations, being reduplicated to 6–8 thickened, tangled strands.

The Effect of a Broad-Spectrum Sunscreen on SSR Photodamage

The BS-SS was very effective in reducing the photodamage produced by SSR. Cyst proliferation was prevented (Fig 2*f*). Only 1 out of 6 specimens showed a mild proliferation to 2–3 rows. The collagen-containing upper dermis was slightly thickened but bundles remained randomly arrayed. There was no decrease in Van Gieson's staining. Cellularity was moderate with slightly more fibroblasts and lymphocytes than normal; massive inflammation did not occur. Mast cells were not increased although they did tend to be larger than normal.

Elastosis was prevented (Fig 3*l*). With a very mild elastic fiber hyperplasia, specimens often resembled normal controls. All 3 histochemical stains showed GAGs slightly but not remarkably increased compared to normal.

The panniculus (Fig 2*f*) and elastic sheath were unchanged.

DISCUSSION

There is compelling evidence that UVA radiation, long considered innocuous, is capable of inducing profound photodamage within the dermis [6–8]. Furthermore, epidermal tumors can be induced by UVA [4,5], an observation that was also made in this study. We have now shown that UVA, in amounts reasonably obtainable from solar irradiation can, like UVB, produce elastosis, elevate GAGs, and cause hypertrophy of deeply located tissue. It can also add to the photodamage induced by UVB.

The seemingly paradoxical observation that the "low" dose (3000 J/cm^2) of UVA from the xenon source was far more destructive than the "high" dose (13,000 J/cm^2) from the black lights can probably be explained by the different spectral power distribution of the 2 UVA sources (Fig 1). The WG 345-filtered xenon source provides, like sunlight, radiation rich in the shorter wavelengths (315–340 nm). The spectrum of the Mylar-filtered black lights, deficient in these wavelengths, extends primarily from 340–400 nm (peak ~365 nm). It should be noted that the elastosis produced in naked mice by Berger and coworkers was with a black light source [6] and required huge doses (>20,000 J/cm^2). Thus, it is insufficient to attribute a result at a specific dose to the entire waveband. Of great importance is the spectral distribution of the radiation source. This study also stresses the need for action spectra with regard to the chronic effects of UVA.

Some animals from the UVA-BL group were biopsied after a cumulative dose of ~5,600 J/cm^2 to assess the effect of 1000

times more UVA than UVB. These specimens were almost indistinguishable from unirradiated controls. Only a very mild elastic fiber hyperplasia was noted. This suggests that the enhanced photodamage produced by SSR supplemented with UVA from the black light source was due, mainly, to the 560 J/cm^2 of UVA from the xenon source itself. Although this does not rule out a possible photoaugmentation effect by the ~2900 J/cm^2 of the longer wavelengths emitted by the black lights, it does make rather unlikely an effect on photodamage by the tiny amount of UVA emitted by FS-20 bulbs in this and earlier studies [1,18]. FS-20 bulbs also emit a small amount of UVC radiation (270–280 nm). Although UVC can add to erythema and epidermal damage [19], we have evidence that it does not contribute to dermal photodamage. Animals irradiated with and without a cellulose triacetate film (which attenuates UVC) had equivalent dermal damage (unpublished results).

With regard to the small amount of UVB (300–315 nm) present in the WG 345-filtered xenon source, it is possible that these wavelengths could have contributed to the observed changes. However, the striking differences between the UVB- and UVA-irradiated specimens make this unlikely. It is also unlikely that heat played a role in these changes. Temperature at the skin's surface, measured throughout the exposure time on a weekly basis, did not exceed 35°C. Furthermore, exposure of hairless mice to infrared radiation (~1900 J/cm^2 total; 40°C) for up to a year failed to damage connective tissue and produced only mild elastic fiber hyperplasia (unpublished results).

The lack of collagen damage by UVA was notable. While UV radiation might damage collagen directly [20], most changes are probably indirect through enzymatic digestion. The latter has been proposed by Lovell [21] as the major effect of UV on collagen in vivo. Tumor cells [22,23] and inflammatory infiltrates [24,25] are known to release proteolytic enzymes capable of digesting collagen. In UVB- and SSR-irradiated animals, both inflammation and collagen damage were severe. In contrast to the perivenular neutrophilic infiltrate reported by Gilchrest et al [7] in humans after acute UVA exposure, chronic UVA, in our study, was ineffectual in inducing a dermal infiltrate. This and the extremely small tumor load in UVA-irradiated animals provide a likely explanation for the lack of collagen damage. Berger, Tsambaos, and Kaase [6] also saw no collagen damage and no inflammation in their UVA-irradiated naked mice.

These findings justify the concerns of dermatologists and photobiologists [26–28] about the adverse effects of UVA on the skin. While it is important to appreciate that UVA is photodamaging, in reality it is inseparable from UVB. Solar radiation includes both wavebands. Summation effects, described in the study, are the real concern. For example, PUVA therapy using dominantly UVA, but containing up to 10% UVB, is given on top of prior and continuing solar exposure. Habitués of tanning parlors are also at risk in adding to prior photodamage. Another potential source of increased UVA radiation is the widespread use of sunscreens that are only UVB absorbers. Longer hours in the sun, without fear of burning, allow the accumulation of far higher doses of UVA than is normally possible. In June, at 40°N latitude, a 1-h exposure at midday will provide ~10 J/cm^2 UVA. Hence, 1 h a day for 2–3 months in 4 consecutive years would result in an accumulation of 3000 J/cm^2, the dose found severely damaging in this study.

The sunscreen studied herein contained a PABA ester and the benzophenone derivative oxybenzone, extending the absorption spectrum further into the UVA waveband [29]. We have shown previously that these sunscreens provide excellent protection against UVB radiation [1,18]. Broader protection may, however, be needed against UVA, especially in the mid-range 330–350 nm, a region not sufficiently filtered out by currently available sunscreens.

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